

WE CLAIM:

1. A process for identifying a ligand to a target biomolecule comprising,
  - a) obtaining a target biomolecule crystal;
  - b) exposing the target biomolecule crystal to one or more test samples;  
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  - c) obtaining an X-ray crystal diffraction pattern to determine whether a ligand/receptor complex is formed.
- 10 2. The process according to Claim 1 further comprising the steps of obtaining an X-ray crystal diffraction pattern of the target biomolecule crystal prior to exposure to the test samples and comparing the X-ray diffraction pattern of the target molecule before and after the exposure.
- 15 3. The process according to Claim 1 further comprising the step of transforming diffraction pattern into an electron density map.
4. The process according to Claim 3 further comprising the step of converting electron density map into a structure.
- 20 5. The process according to Claim 1, wherein the target biomolecule is exposed to a test sample by soaking the target biomolecule crystal in a solution that contains the test sample.
- 25 6. The process according to Claim 1, wherein the target biomolecule is exposed to the test samples by soaking the target biomolecule crystal in a solution containing a mixture of test samples.

7. The process according to Claim 1, wherein the target biomolecule is exposed to the test sample by co-crystallizing the target biomolecule crystal with a test sample.
- 5 8. The process according to Claim 1, wherein the target biomolecule is exposed to the test samples by co-crystallizing the target biomolecule crystal with a mixture of test samples.
9. The process according to Claim 6, wherein the mixture of test samples are diversely shaped.
- 10 10. The process according to Claim 8, wherein the mixture of test samples are diversely shaped.
11. The process according to Claim 1 wherein the ligand is a biologically-active moiety.
- 15 12. The process according to Claim 1, wherein the target is a polypeptide.
13. The process according to Claim 1, wherein the target is a re-engineered polypeptide.
- 20 14. A biologically-active moiety identified by the process according to Claim 11.
15. The process according to Claim 1 wherein said ligand is a lead compound.
16. A process to design a ligand for a target biomolecule comprising,  
25 a) obtaining a target biomolecule crystal;  
b) identifying at least two ligands to the target biomolecule by X-ray crystallographic screening;

- c) determining the spatial orientation of the ligands when they are bound to the target biomolecule; and
- d) linking the ligands together according to the spatial orientation to form the ligand.

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17. The process according to Claim 16 wherein the spatial orientation of the bound ligands is determined by forming a multi-ligand/target molecule complex and generating an X-ray crystal structure of the multi-ligand/target molecule complex.

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18. The process according to Claim 16 wherein one ligand is bound to the target molecule before another ligand is bound to the target molecule.

19. The process according to Claim 16 wherein the ligand is a biologically-active moiety.

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20. The process according to Claim 16, wherein the target is a polypeptide.

21. The process according to Claim 16, wherein the target is a re-engineered polypeptide.

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22. A biologically-active moiety designed by the process according to Claim 19.

23. The process according to Claim 16 wherein said ligand is a lead compound.

24. A process to design a ligand for a target biomolecule comprising,

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- a) obtaining a target biomolecule crystal;
- b) identifying a ligand to the target biomolecule by X-ray crystallographic screening;

c) making derivatives of the ligand.

25. The process according to Claim 24 wherein said ligand is a lead compound.

5 26. The process according to Claim 24 wherein the ligand is a biologically-active compound.

27. The process according to Claim 24, wherein the target is a polypeptide.

10 28. The process according to Claim 24, wherein the target is a re-engineered polypeptide.

29. A lead compound identified by the process of Claim 25.

30. A biologically-active compound designed by the process according to Claim 25.

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31. A biologically-active compound designed by the process according to Claim 26.

32. A process to form a crystal having an easily accessible active site from a biomolecule comprising,

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a) co-crystallizing the biomolecule with a degradable ligand; and

b) degrading the ligand once the crystal is formed.

33. The process according to Claim 32 wherein the biomolecule active site degrades the ligand.

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34. The process according to Claim 32 further comprising adding degradation agents to degrade the ligand.

35. The process according to Claim 32 wherein said ligand spontaneously degrades.